APPLN FILING DATE: OCT. 5, 2001 033053-025 TITLE: BILE-ACID DERIVED COMPOUNDS FOR PROVIDING SUSTAINED SYSTEMIC CONCENTRA-TIONS OF DRUGS AFTER ORAL ADMINISTRATION

INVENTOR: KENNETH C. CUNDY ET AL. APPLICATION SERIAL NO: 09/972,425

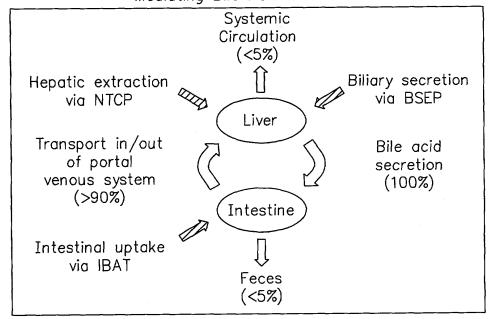
1 OF 31



1/31

FIG. 1

FIG. 2The Enterohepatic Circulation with Key Transporter Proteins
Mediating Bile Acid Circulation



APPLN FILING DATE: OCT. 5, 2001 033053-025
TITLE: BILE-ACID DERIVED COMPOUNDS FOR
PROVIDING SUSTAINED SYSTEMIC CONCENTRATIONS OF DRUGS AFTER ORAL ADMINISTRATION
INVENTOR: KENNETH C. CUNDY ET AL.
APPLICATION SERIAL NO: 09/972,425 2 of 31

2/31

FIG. 3

Bile Acid Conjugates of HMG-CoA Reductase Inhibitor

FIG. 4 ${\stackrel{R}{\scriptstyle _{1}}}_{2}$ НО (V) H0'''' (VI) $Z = CO_2H, P(0)(OR^{19})(OH)$ H0,,,, (VII) ${\tt R}_2$ $Z = SO_3H, P(0)(OR^{19})(OH),$ OSO_3H , $OP(O)(OR^{19})(OH)$ НО,,,,, R_1 (VIII)

R1 =
$$\alpha$$
-OH; R2 = α -OH (Cholate)
R1 = β -OH; R2 = H (Ursodeoxycholate)
R1 = α -OH; R2 = H (Chenodeoxycholate)
R1 = H; R2 = α -OH (Deoxycholate)
R1 = β -OH; R2 = α -OH (Ursocholate)
R1 = H; R2 = H (Lithocholate)

APPLN FILING DATE: OCT. 5, 2001 033053-025
TITLE: BILE-ACID DERIVED COMPOUNDS FOR
PROVIDING SUSTAINED SYSTEMIC CONCENTRATIONS OF DRUGS AFTER ORAL ADMINISTRATION
INVENTOR: KENNETH C. CUNDY ET AL.
APPLICATION SERIAL NO: 09/972,425 4 OF 31

FIG. 5

Plant Production of the production of th

$$R_{1}$$
 R_{2}
 R_{3}
 R_{1}
 R_{2}
 R_{3}
 R_{1}
 R_{1}
 R_{2}
 R_{3}
 R_{1}
 R_{2}
 R_{3}
 R_{1}
 R_{2}
 R_{3}
 R_{1}
 R_{1}
 R_{2}
 R_{3}
 R_{1}
 R_{1}
 R_{2}
 R_{3}
 R_{1}
 R_{2}
 R_{3}
 R_{4}
 R_{1}
 R_{4}
 R_{4}
 R_{4}
 R_{4}
 R_{1}
 R_{2}
 R_{3}
 R_{4}
 R_{4}
 R_{4}
 R_{4}
 R_{4}
 R_{4

R1 = α -OH; R2 = α -OH (Cholate) R1 = β -OH; R2 = H (Ursodeoxycholate) R1 = α -OH; R2 = H (Chenodeoxycholate) R1 = H; R2 = α -OH (Deoxycholate) R1 = β -OH; R2 = α -OH (Ursocholate) R1 = H; R2 = H (Lithocholate) APPLN FILING DATE: OCT. 5, 2001 033053-025
TITLE: BILE-ACID DERIVED COMPOUNDS FOR
PROVIDING SUSTAINED SYSTEMIC CONCENTRA-TIONS OF DRUGS AFTER ORAL ADMINISTRATION INVENTOR: KENNETH C. CUNDY ET AL.

APPLICATION SERIAL No: 09/972,425

5 OF 31

5/31

FIG. 6

$$R^{23}_{R^{24}} \circ R^{5'}_{R^{7'}} R^{6'}_{R^{9'}} R^{10'}_{R^{11'}}$$
 $R^{23}_{R^{24}} \circ R^{5'}_{R^{7'}} R^{8'}_{R^{11'}}$
 $R^{23}_{R^{24}} \circ R^{5'}_{R^{7'}} R^{6'}_{R^{9'}} R^{10'}_{R^{11'}}$
 $R^{23}_{R^{24}} \circ R^{5'}_{R^{7'}} R^{6'}_{R^{9'}} R^{10'}_{R^{11'}}$
 $R^{23}_{R^{24}} \circ R^{5'}_{R^{7'}} R^{6'}_{R^{9'}} R^{10'}_{R^{11'}}$
 $R^{2}_{R^{23}} R^{24} \circ R^{5'}_{R^{7'}} R^{6'}_{R^{9'}} R^{10'}_{R^{11'}}$
 $R^{2}_{R^{23}} R^{24} \circ R^{5'}_{R^{7'}} R^{8'}_{R^{9'}} R^{11'}_{R^{11'}}$
 $R^{2}_{R^{23}} R^{24} \circ R^{5'}_{R^{9'}} R^{10'}_{R^{11'}}$
 $R^{2}_{R^{23}} R^{24} \circ R^{5'}_{R^{9'}} R^{10'}_{R^{11'}}$

R1 = α -OH; R2 = α -OH (Cholate)

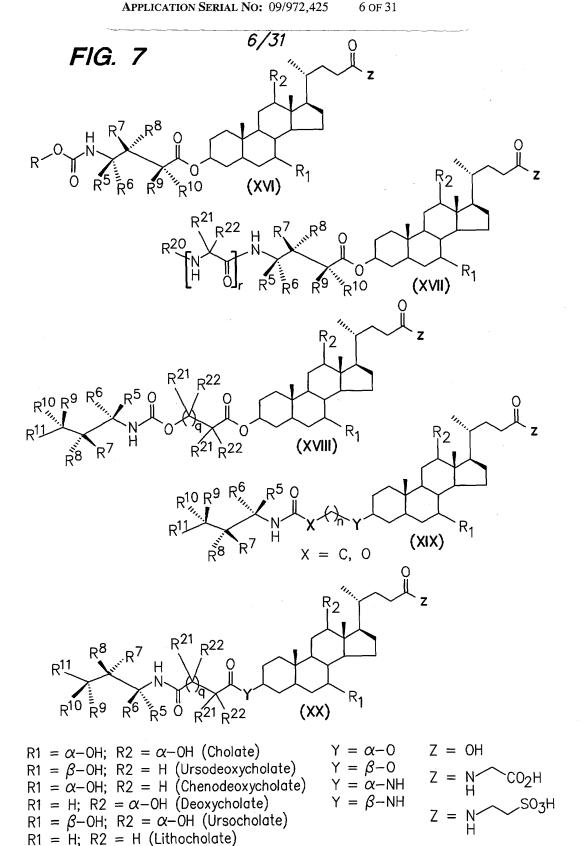
 $R1 = \beta - OH$; R2 = H (Ursodeoxycholate)

 $R1 = \alpha - OH$; R2 = H (Chenodeoxycholate)

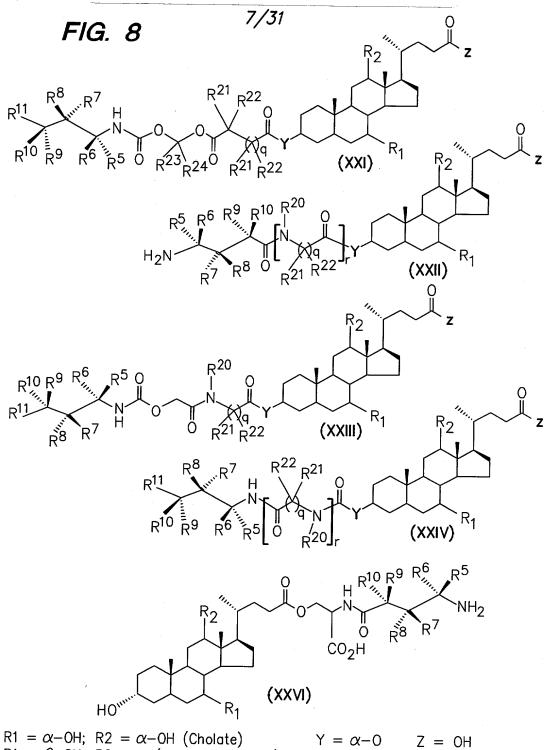
R1 = H; R2 = α -OH (Deoxycholate)

R1 = β -OH; R2 = α -OH (Ursocholate) R1 = H; R2 = H (Lithocholate)

APPLN FILING DATE: OCT. 5, 2001 033053-025
TITLE: BILE-ACID DERIVED COMPOUNDS FOR
PROVIDING SUSTAINED SYSTEMIC CONCENTRATIONS OF DRUGS AFTER ORAL ADMINISTRATION
INVENTOR: KENNETH C. CUNDY SET AL.



TITLE: BILE-ACID DERIVED COMPOUNDS FOR PROVIDING SUSTAINED SYSTEMIC CONCENTRA-TIONS OF DRUGS AFTER ORAL ADMINISTRATION INVENTOR: KENNETH C. CUNDY ET AL.
APPLICATION SERIAL NO: 09/972,425 7 OF 31

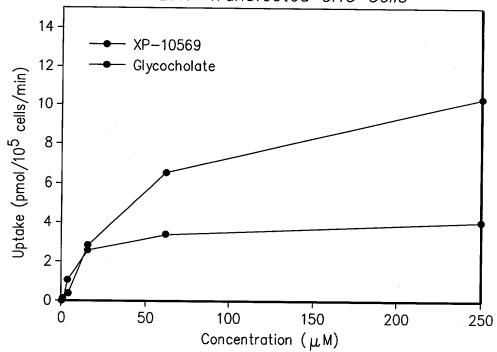


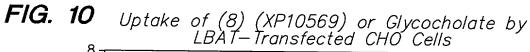
 $R1 = \beta - OH$; R2 = H (Ursodeoxycholate) $Y = \beta - 0$ R1 = α -OH; R2 = H (Chenodeoxycholate) $Y = \alpha - NH$ R1 = H; R2 = α -OH (Deoxycholate) $Y = \beta - NH$ R1 = β -OH; R2 = α -OH (Úrsocholáte)

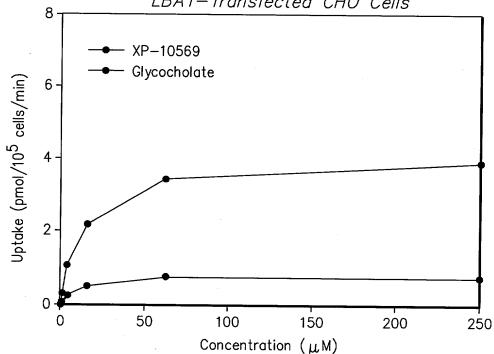
R1 = H; R2 = H (Lithocholate)

APPLN FILING DATE: OCT. 5, 2001 TITLE: BILE-ACID DERIVED COMPOUNDS FOR PROVIDING SUSTAINED SYSTEMIC CONCENTRA-TIONS OF DRUGS AFTER ORAL ADMINISTRATION INVENTOR: KENNETH C. CUNDY ET AL. APPLICATION SERIAL NO: 09/972,425 8 of 31

8/31 **FIG. 9** Uptake of (8) (XP10569) or Glycochocholate by IBAT—Transfected CHO Cells







APPLING DATE: UCT. 5, 2001 033053-025
TITLE: BILE-ACID DERIVED COMPOUNDS FOR
PROVIDING SUSTAINED SYSTEMIC CONCENTRATIONS OF DRUGS AFTER ORAL ADMINISTRATION
INVENTOR: KENNETH C. CUNDY ET AL.
APPLICATION SERIAL NO: 09/972,425 9 OF 31

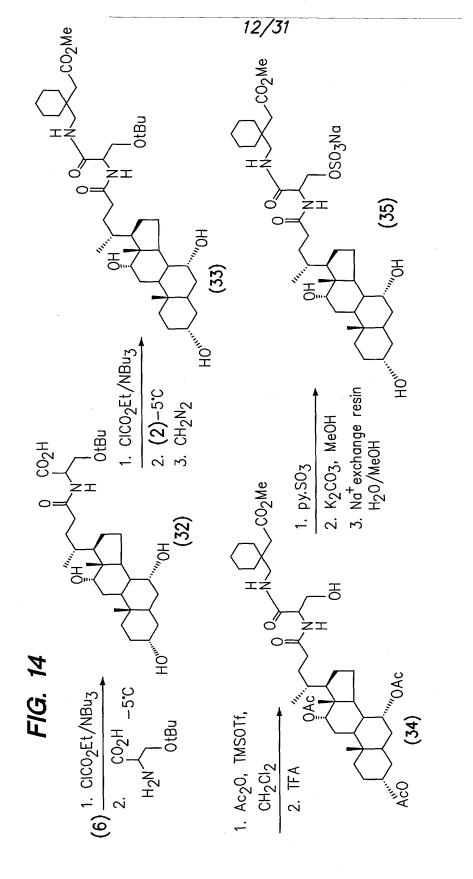
APPLN FILING DATE: OCT. 5, 2001 033053-025
TITLE: BILE-ACID DERIVED COMPOUNDS FOR
PROVIDING SUSTAINED SYSTEMIC CONCENTRATIONS OF DRUGS AFTER ORAL ADMINISTRATION
INVENTOR: KENNETH C. CUNDY ET AL.
APPLICATION SERIAL NO: 09/972,425 10 of 31

TITLE: BILE-ACID DERIVED COMPOUNDS FOR PROVIDING SUSTAINED SYSTEMIC CONCENTRATIONS OF DRUGS AFTER ORAL ADMINISTRATION INVENTOR: KENNETH C. CUNDY ET AL.

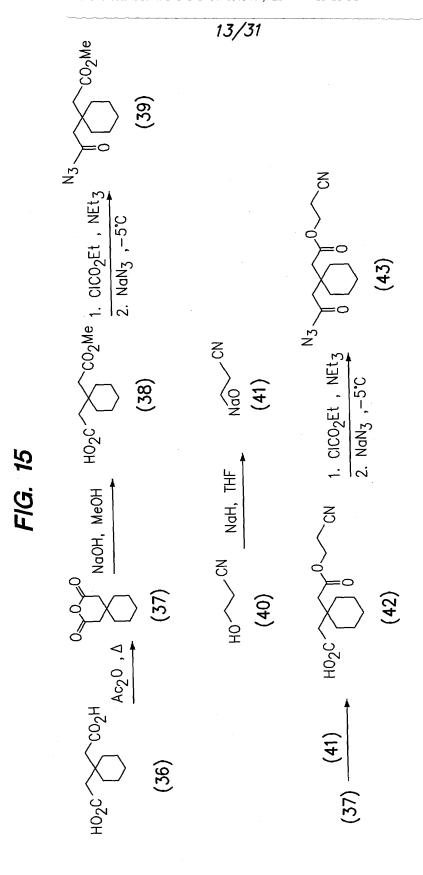
APPLICATION SERIAL NO: 09/972,425 11 of 31

11/31 ²200 ő 0= (28)HOmmoH 1. CICO₂Et/NBu₃ Na⁺exchange resin H2O/MeOH 2. **(2)**–5°C ď FIG. 13 (6) 1. CICO₂Et/NBu₃ (53) CH_2N_2 HOMM

APPLN FILING DATE: OCT. 5, 2001 033053-025
TITLE: BILE-ACID DERIVED COMPOUNDS FOR
PROVIDING SUSTAINED SYSTEMIC CONCENTRATIONS OF DRUGS AFTER ORAL ADMINISTRATION
INVENTOR: KENNETH C. CUNDY ET AL.
APPLICATION SERIAL NO: 09/972,425 12 of 31



APPLN FILING DATE: OCT. 5, 2001 033053-025
TITLE: BILE-ACID DERIVED COMPOUNDS FOR
PROVIDING SUSTAINED SYSTEMIC CONCENTRATIONS OF DRUGS AFTER ORAL ADMINISTRATION
INVENTOR: KENNETH C. CUNDY ET AL.
APPLICATION SERIAL NO: 09/972,425 13 of 31



TITLE: BILE-ACID DERIVED COMPOUNDS FOR PROVIDING SUSTAINED SYSTEMIC CONCENTRATIONS OF DRUGS AFTER ORAL ADMINISTRATION INVENTOR: KENNETH C. CUNDY ET AL.

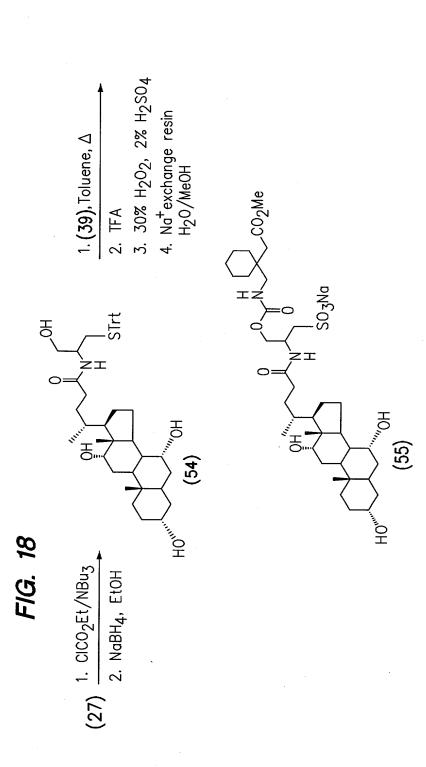
APPLICATION SERIAL NO: 09/972,425 14 of 31

14/31

HO (214)H0.... 1. KOAc, 18-crown-6 DMSO 2. NdOH, H₂0 Piperidine ".0Ac (213)Phl(0Ac)₂ 1. Ac20 ,py 7 Toluene, Δ (212).... HO....

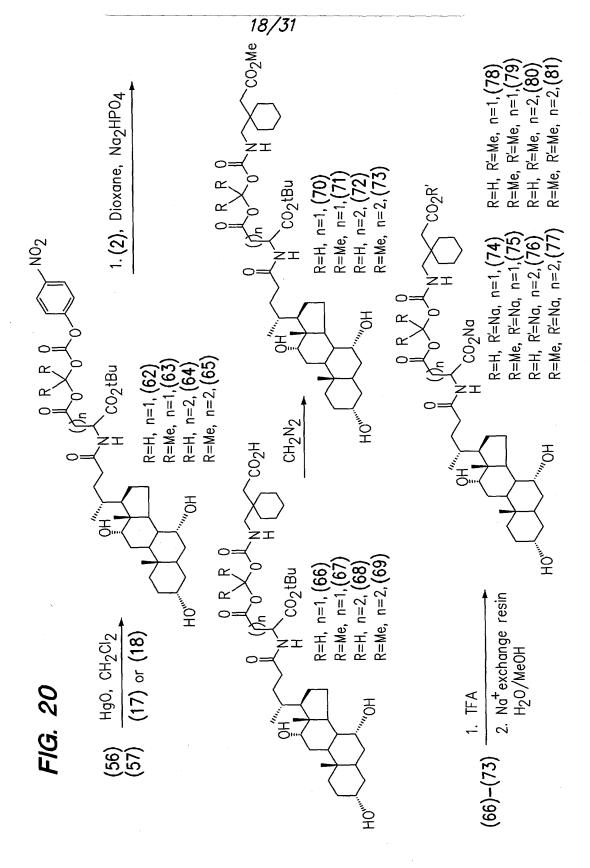
and the first and the forest and the forest and the first level took an

APPLN FILING DATE: OCT. 5, 2001 033053-025
TITLE: BILE-ACID DERIVED COMPOUNDS FOR
PROVIDING SUSTAINED SYSTEMIC CONCENTRATIONS OF DRUGS AFTER ORAL ADMINISTRATION
INVENTOR: KENNETH C. CUNDY ET AL.
APPLICATION SERIAL NO: 09/972,425 15 of 31



APPLN FILING DATE: OCT. 5, 2001 033053-025
TITLE: BILE-ACID DERIVED COMPOUNDS FOR
PROVIDING SUSTAINED SYSTEMIC CONCENTRATIONS OF DRUGS AFTER ORAL ADMINISTRATION
INVENTOR: KENNETH C. CUNDY ET AL.
APPLICATION SERIAL NO: 09/972,425 17 of 31

APPLN FILING DATE: OCT. 5, 2001 033053-025 TITLE: BILE-ACID DERIVED COMPOUNDS FOR PROVIDING SUSTAINED SYSTEMIC CONCENTRA-TIONS OF DRUGS AFTER ORAL ADMINISTRATION INVENTOR: KENNETH C. CUNDY ET AL. APPLICATION SERIAL NO: 09/972,425 18 of 31



APPLN FILING DATE: OCT. 5, 2001 033053-025
TITLE: BILE-ACID DERIVED COMPOUNDS FOR
PROVIDING SUSTAINED SYSTEMIC CONCENTRATIONS OF DRUGS AFTER ORAL ADMINISTRATION
INVENTOR: KENNETH C. CUNDY ET AL.
APPLICATION SERIAL NO: 09/972,425 19 of 31

20/31

Y=3 α -0 (96) Y=3 β -0 (97) Y=3 α -NH (98) Y=3 β -NH (99) $3\alpha - 0$ (102) $3\beta - 0$ (103) 0 ,,,OH 10,10H n=1-5 Y=3 α -0 (92) Y=3 β -0 (93) Y=3 α -NH (94) Y=3 β -NH (95) $3\alpha - 0$ (100) $3\beta - 0$ (101) n=1-5

Compounds (92)-(103) prepared following methods described in co-pending application "Bile Acid-Derived Compounds for Enhancing Oral Absorption and Systemic Bioavailability of Drugs" assigned to XenoPort, Inc.

APPLN FILING DATE: OCT. 5, 2001 033053-025
TITLE: BILE-ACID DERIVED COMPOUNDS FOR
PROVIDING SUSTAINED SYSTEMIC CONCENTRATIONS OF DRUGS AFTER ORAL ADMINISTRATION
INVENTOR: KENNETH C. CUNDY ET AL.
APPLICATION SERIAL NO: 09/972,425 21 of 31

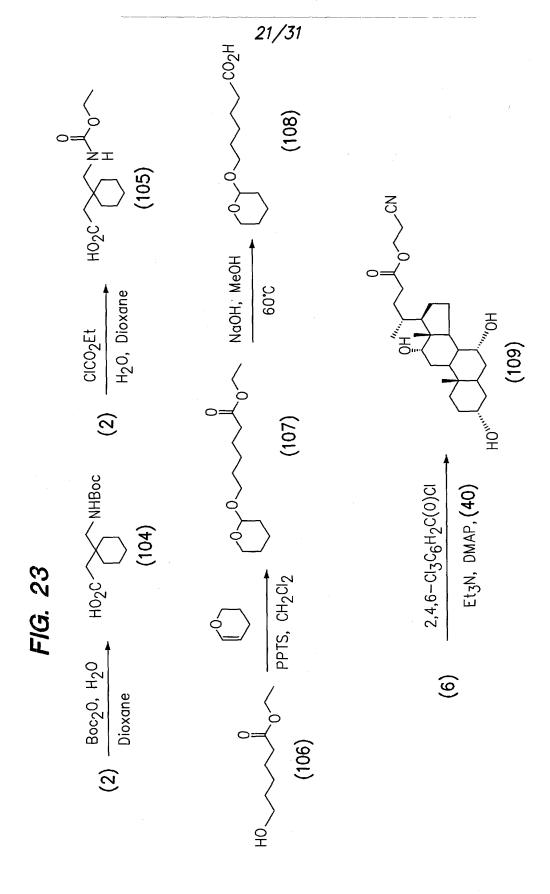


FIG. 24

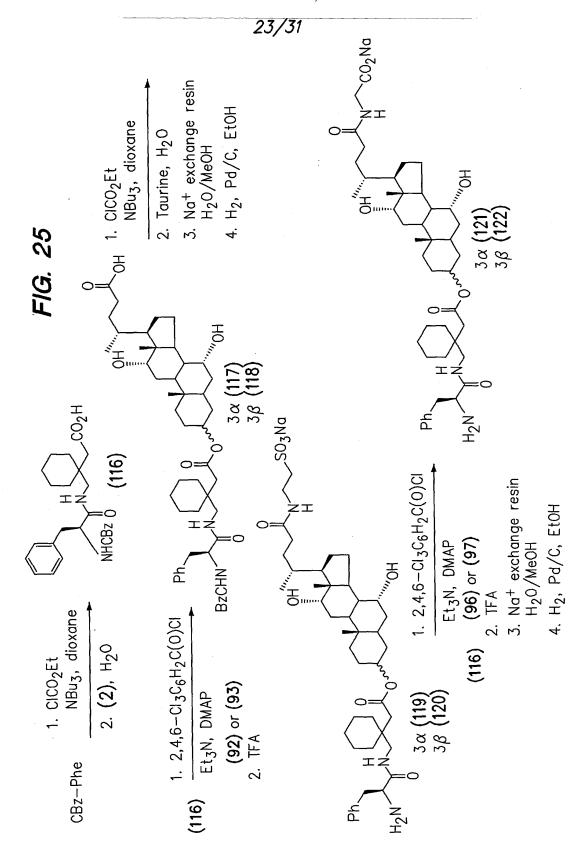
1. $2,4,6-\text{Cl}_3\text{C}_6\text{H}_2\text{C}(0)\text{Cl}$

(105)

SO3Na

(105)
$$\begin{array}{c} 1. \ 2,4,6-\text{Cl}_3\text{C}_6\text{H}_2\text{C}(0)\text{Cl} \\ \hline \text{Et}_3\text{N}, \ \text{DMAP} \\ \hline (96) \ \text{or} \ (97) \\ \hline 2. \ \text{TFA} \end{array}$$

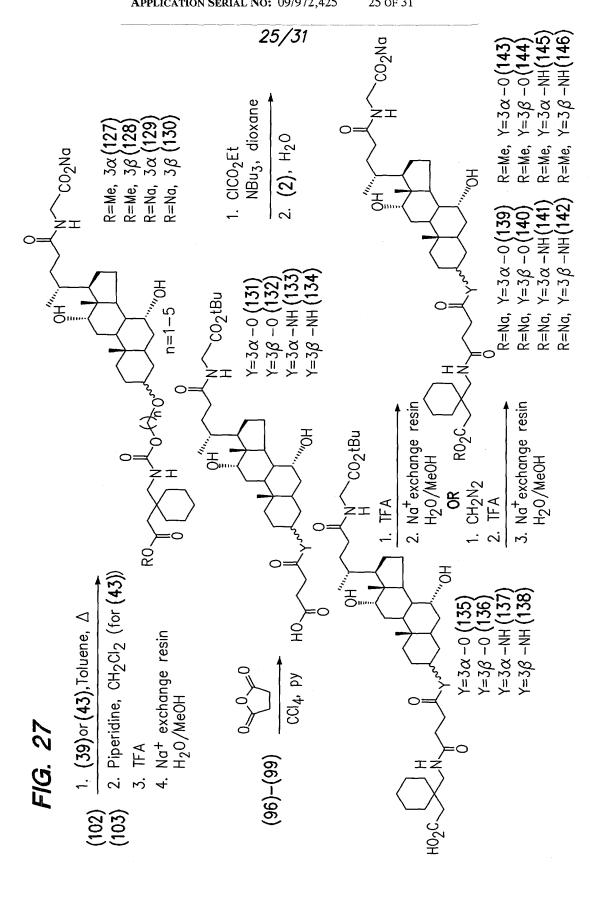
APPLN FILING DATE: OCT. 5, 2001 033053-025
TITLE: BILE-ACID DERIVED COMPOUNDS FOR
PROVIDING SUSTAINED SYSTEMIC CONCENTRATIONS OF DRUGS AFTER ORAL ADMINISTRATION
INVENTOR: KENNETH C. CUNDY ET AL.
APPLICATION SERIAL NO: 09/972,425 23 of 31



APPLN FILING DATE: OCT. 5, 2001 033053-025
TITLE: BILE-ACID DERIVED COMPOUNDS FOR
PROVIDING SUSTAINED SYSTEMIC CONCENTRATIONS OF DRUGS AFTER ORAL ADMINISTRATION
INVENTOR: KENNETH C. CUNDY ET AL.
APPLICATION SERIAL NO: 09/972,425 24 of 31

| | 24/31 | o Z |
|---|--|---|
| 1. PPTs, MeOH, ∆ 2. (39), Toluene, ∆ 3. TFA | 1. (39). Toluene, Δ 2. Piperidine, CH_2CI_2 | OH N SO3NQ (126) |
| FIG. 26 OH N CO2 tBu (123) | 0H ^M CO ₂ H (109) (124) (109) | O 1. CICO ₂ Et NBu ₃ , dioxane 2. Taurine, H ₂ O 3. Na ⁺ exchange resin H ₂ O/MeOH S) XP10745 O O O O O O O O O O O O O O O O O O O |
| FIG 2,4,6-Cl ₃ C ₆ H ₂ C(0)Cl Et ₃ N, DMAP, (108) | ДНТ — 0 — 1 — 0 — 0 — 0 — 0 — 0 — 0 — 0 — 0 | 0 (125) 0 H (125) 0 KP1 |

APPLN FILING DATE: OCT. 5, 2001 U53053-025
TITLE: BILE-ACID DERIVED COMPOUNDS FOR
PROVIDING SUSTAINED SYSTEMIC CONCENTRATIONS OF DRUGS AFTER ORAL ADMINISTRATION
INVENTOR: KENNETH C. CUNDY ET AL.
APPLICATION SERIAL NO: 09/972,425 25 of 31



APPLN FILING DATE: OCT. 5, 2001 033053-025
TITLE: BILE-ACID DERIVED COMPOUNDS FOR
PROVIDING SUSTAINED SYSTEMIC CONCENTRATIONS OF DRUGS AFTER ORAL ADMINISTRATION
INVENTOR: KENNETH C. CUNDY ET AL.
APPLICATION SERIAL NO: 09/972,425 26 of 31

26/31

R'=Me, R=Me, Y= 3α -0(155) R'=Me, R=Me, Y= 3β -0(156) R'=Me, R=Me, Y= 3α -NH(157 1. **(2)**, Dioxane, Na₂HPO₄ Y=38-NH 4. Na⁺exchange resin H₂O/MeOH 2. Optionally CH₂N₂ R=Me, R'=Me, Y=3α-NH (153 $Y=3\beta-NH$ (154) (151)(152) $\gamma=3\beta-0$ Y=3α-0 (0 R'=Me, R=H, 'R'=Me, R=H, ' R=H, R′=Me, R=H, $Y=3\beta-NH(142)$ Y=3α -NH**(141** "OH R'=Me, I $\gamma=3\alpha-0$ $Y=3\beta-0$ R'=Na, R=Me, Y=3 α -NH(149) $Y=3\beta-NH(150)$ R=Me, R=Me, R=Me, R=Me, R'=Na, R=Me, Y=3 β -0 (148)Y=3α-0**(14**7 R=Me, R=Me, $Y=3\alpha-NH$ $Y=3\beta-NH$ $Y=3\beta-0$ Y=3α-0 K'=Na, K′=Na, FIG. 28 R=H, R=H, R=H, R=H, , $Y=3\beta-0$ (144) $Y=3\alpha-NH$ (145) Y=3 β -NH (146) Y=3α-0 **(143** Hgo, CH₂Cl₂ R=H, R=H, R=H, R=H, R'=Na, I R'=Na, R'=Na, R′=Na, (56)

APPLN FILING DATE: OCT. 5, 2001 033053-025 TITLE: BILE-ACID DERIVED COMPOUNDS FOR PROVIDING SUSTAINED SYSTEMIC CONCENTRA-TIONS OF DRUGS AFTER ORAL ADMINISTRATION INVENTOR: KENNETH C. CUNDY ET AL. APPLICATION SERIAL NO: 09/972,425 27 of 31

27/31

APPLN FILING DATE: OCT. 5, 2001 033053-025 TITLE: BILE-ACID DERIVED COMPOUNDS FOR PROVIDING SUSTAINED SYSTEMIC CONCENTRA-TIONS OF DRUGS AFTER ORAL ADMINISTRATION INVENTOR: KENNETH C. CUNDY ET AL. APPLICATION SERIAL NO: 09/972,425 28 of 31

R'=Na,

 $Y=3\beta-NH(207)$

R=Et,

R′=Na,

 $Y=3\beta-NH(203)$

R=Bn

R′=Me,

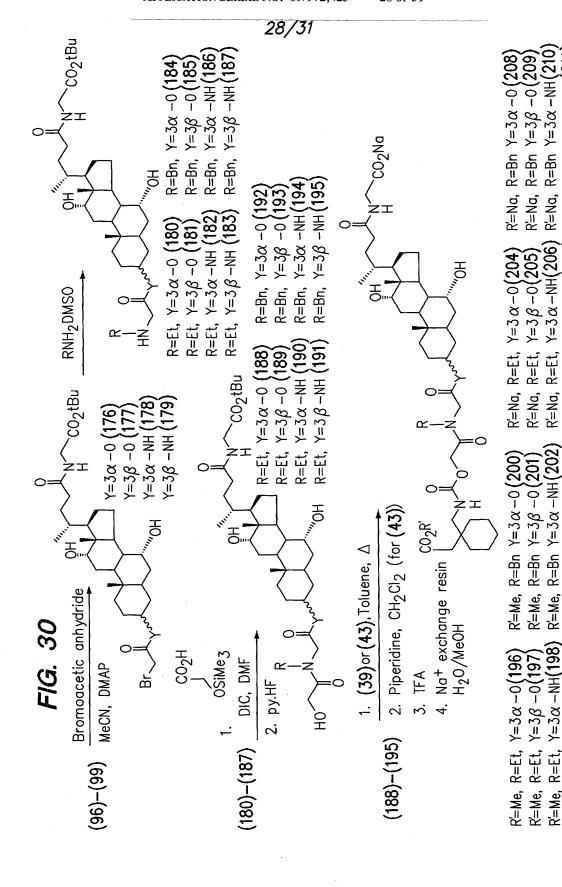
Y=3β-NH**(199**)

R=Et,

R′=Me,

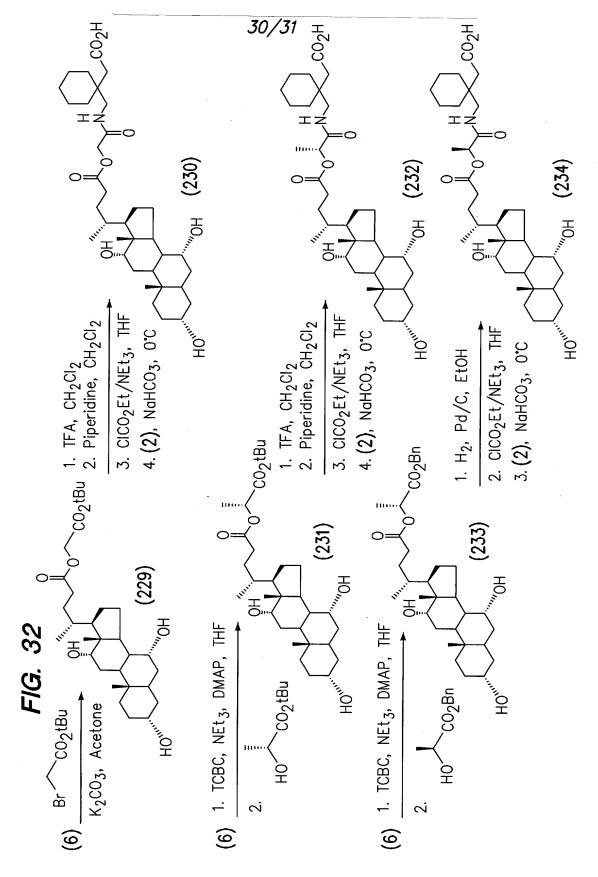
R=Et,

R′=Me,



APPLN FILING DATE: OCT. 5, 2001 033053-025 TITLE: BILE-ACID DERIVED COMPOUNDS FOR PROVIDING SUSTAINED SYSTEMIC CONCENTRA-TIONS OF DRUGS AFTER ORAL ADMINISTRATION INVENTOR: KENNETH C. CUNDY ET AL. APPLICATION SERIAL NO: 09/972,425 29 of 31

APPLN FILING DATE: OCT. 5, 2001 033053-025
TITLE: BILE-ACID DERIVED COMPOUNDS FOR
PROVIDING SUSTAINED SYSTEMIC CONCENTRATIONS OF DRUGS AFTER ORAL ADMINISTRATION
INVENTOR: KENNETH C. CUNDY ET AL.
APPLICATION SERIAL NO: 09/972,425 30 of 31



APPLN FILING DATE: OCT. 5, 2001 033053-025
TITLE: BILE-ACID DERIVED COMPOUNDS FOR
PROVIDING SUSTAINED SYSTEMIC CONCENTRATIONS OF DRUGS AFTER ORAL ADMINISTRATION
INVENTOR: KENNETH C. CUNDY ET AL.
APPLICATION SERIAL NO: 09/972,425 31 of 31

31/31 NaOH/MeOH